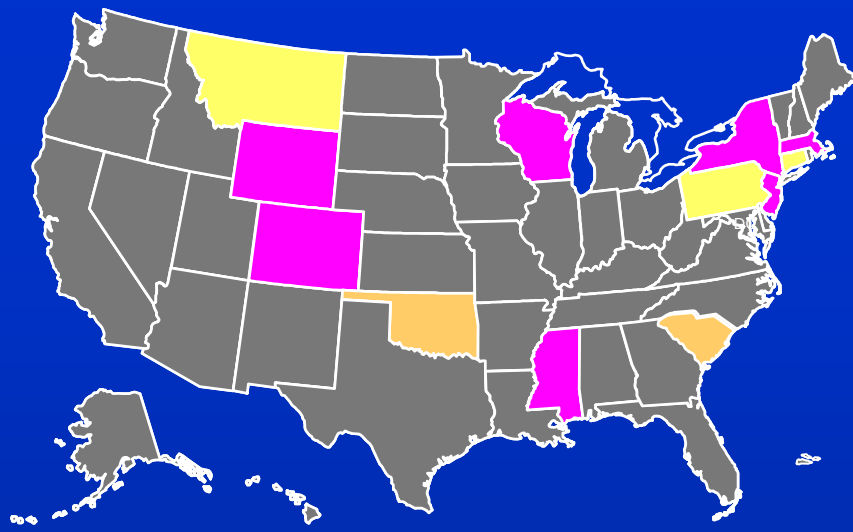
Evaluating the Health Outcomes from Newborn Screening for Cystic Fibrosis

Scott Grosse, PhD
Public Health Assessment of Genetic Tests for Screening and Prevention
September 27, 2004

Centers for Disease Control and Prevention

National Center on Birth Defects
and Developmental Disabilities

Public Health Context



- About 20% of U.S. infants are screened for cystic fibrosis (CF)
- State by state decision, mostly since 1999
- No national public health consensus
- CDC workshops
  - 1997 – insufficient evidence for routine screening
  - 2003 – evidence of moderate benefit

Time Line

- January 1997 workshop convened by CDC & partners
- December 1997 MMWR Reports & Recommendations
  - Encourage pilot screening and research
  - Collect evidence on additional outcomes
  - Convene panel in 2 years to review new evidence
- May 2002 – CF Foundation proposes new workshop
- January 2003 – CDC/NCBDDD considers workshop
- April 2003 – Experts visit CDC to present evidence
- November 2003 – Workshop convened by CDC & CFF
- October 2004 – MMWR Reports & Recommendations

Age of Diagnosis in United States

- About 25% of children with CF are diagnosed soon after birth in absence of NBS
  - Meconium ileus
  - Prenatal diagnosis, family history, etc.
- Median age of diagnosis for others is 14 months
- With newborn screening (NBS), diagnosis is feasible within 1-2 months, about 12 months sooner

Arguments for Screening Infants for CF

- Clinical utility – improved outcomes
- Prevent diagnostic odyssey
- Opportunity for early treatment
  - Pancreatic enzymes
  - Vitamin supplements
  - High-fat dietary regimen
  - More aggressive antibiotic therapy
- Genetic counseling – 1 in 4 risk of recurrence in siblings

Traditional Criteria for NBS

- Clinical utility
  - Prevention of child death or severe disability
  - Model is PKU
- Other criteria
  - Frequency of condition
  - Feasibility and accuracy of screening test in DBS
  - Availability of treatment
  - Cost of screening, etc.
- No consideration of other benefits
  - Reduced morbidity
  - Improved quality of life
  - Benefits to families

Assessing Health Outcomes for CF

- Traditional NBS criteria too narrow
  - CF not associated with intellectual disability
  - Child deaths not common in CF
- Direct clinical outcomes
  - Malnutrition and growth retardation
  - Lung disease
- Indirect outcomes
  - Cognitive development
  - Health-related quality of life (HRQoL)
  - Hospitalizations and burden of treatment
- Balance of outcomes
  - Risks and benefits
  - Cost-effectiveness

Which Health Outcomes Matter Most?

- Those of direct concern to patients and families
- Strength of Recommendation Taxonomy (SORT) (Ebell et al. 2004):
  - Disease-oriented outcomes

    "intermediate, histopathologic, physiologic, or surrogate results…that may or may not reflect improvements in patient outcomes"
  - Patient-oriented outcomes

    "matter directly to patients and help them live longer or better lives, including reduced morbidity, reduced mortality, symptom improvement, improved quality of life, or lower cost"

Classifying Outcomes in CF

- Disease-oriented outcomes – intermediate outcomes measured in routine CF care
  - Growth parameters
  - Lung function and x-rays
- Patient-oriented outcomes
  - Survival
  - Cognitive function
  - Health-related quality of life
  - Hospitalizations, intensive therapies, costs
- Matter of degree
  - Large decrements of direct concern to families
  - Example: growth hormone therapy

Assessing Outcomes at 1997 Workshop

- Evidence from three studies
  - Wisconsin RCT, children born 1985-1994
  - Australia observational study with historical controls, children born 1978-1984
  - Netherlands observational study with nonrandomized controls, children born 1973-1979
- Conclusions
  - Potential biases in both observational studies
  - Consistent evidence of nutritional outcomes
    - Improved height-for-age
    - Reduced growth retardation (below 5th centile)
  - No agreement of sufficient basis for routine NBS
  - Need for evidence on other outcomes (cognitive, HRQoL, cost-effectiveness)

Challenges in Interpreting Evidence: Limitations of Individual Studies

- Biases in observational and some clinical studies
  - Ascertainment bias
  - Differences in genotypes, ethnicity, etc.
  - Differences in care provided
- Randomized controlled trials
  - Chance differences between groups
  - Other threats to validity – contamination
- Common issues
  - Adequate follow-up time and loss to attrition
  - Statistical power – number of observations

Example: Wisconsin RCT

- Well-designed trial – all children screened 1985-1994, randomized to early diagnosis or blinding, 18 year follow-up
- Small numbers of children
  - Screened w/o MI (n=56)
  - Controls w/o MI (n=48)
- Chance difference between groups
  - ΔF508 homozygotes more common in screened group, 59% vs 47% ($p<0.001$)
- Contamination of pulmonary outcomes
  - One center exposed infants to older, infected patients
    - Median age of colonization with *Ps. aeruginosa*
      - 1.0 years for screened children at that center
      - 4.5 years for control children at same center
      - 5.6 years for screened children at other center
  - Poorer pulmonary outcome – greater deterioration of chest x-rays with increasing age in screened group

Example: UK RCT

- Children in Wales and West Midlands randomized to be screened or not, 1985-89
  - Screened (n=58)
  - Not screened (n=44)
- Limitations
  - No standardized treatment protocol
  - Incomplete ascertainment in unscreened cohort
  - Short follow-up: n=19 followed for 4 years
- Outcomes
  - No differences at 4 years (Chatfield et al. 1991)
  - Survival to 5 years (Doull et al. 2001)
    - Ascertained deaths from multiple sources
    - 4 CF-related deaths in unscreened cohort
    - 0 CF-related deaths in screened cohort
    - Difference is significant ($p<0.05$)

Challenges in Interpreting Evidence: Synthesizing Findings

- Statistical significance
  - Individual studies may be under-powered
  - Look for consistency of size of effect
- Assessing bias
  - Are reported prevalences in screened and unscreened groups comparable?
  - Are treatment protocols similar?
  - Is distribution of genotypes similar?
- Inconsistent findings
  - If outcomes depend on treatments provided, no consistent impact of screening may be expected
  - Consider exceptional factors in studies with discrepant findings (e.g. Wisconsin RCT)

Example: French Observational Study (Siret et al., 2003)

- 1989-98 birth cohorts in neighboring regions, excluding children with meconium ileus
  - Brittany, with NBS for CF (n=77)
  - Loire-Atlantique, no NBS for CF (n=36)
- Comparability
  - Same birth prevalence of CF
  - Same treatment protocols
  - ΔF508 homozygotes more common in Brittany (not significantly different)
- Outcomes for Brittany vs Loire-Atlantique
  - CF-related deaths 0/77 vs 3/36 ($p<0.05$)
  - Hospitalization 49% vs 86% ($p<0.0001$)
  - Height-for-age Z-scores 0.3-0.6 higher at 1, 3, 5 years ($p<0.05$)
  - Better chest x-ray and clinical scores ($p<0.05$)
- Consistency: all findings consistent with other studies

Cognitive Outcome in WI RCT: Overall (Koscik et al., 2004)

- Background
  - Malnutrition can affect neurodevelopment
  - Head circumference-for-age lower at diagnosis in control group
- Cognitive assessments
  - Conducted at ages 7-18 years (n=89)
  - Test of Cognitive Skills, 2nd Edition
  - CSI scale (similar to IQ)
- Findings for children without MI (n=71)
  - CSI Mean (SD) not significant (P=0.24)
    - Screened 104.6 (14.4)
    - Controls 99.8 (18.5)
  - No significant correlation of CSI with head circumference (P=0.11)

Cognitive Outcome in WI RCT: Vitamin E (Koscik et al., 2004)

- Fat-soluble vitamin deficiencies common in CF
  - Vitamins A, E, and K
  - About half of children in WI RCT had plasma alpha-tocopherol < 300E at diagnosis – vitamin E deficiency
  - Deficiency corrected by vitamin supplements
- Findings of cognitive assessments (n=66)
  - CSI difference of 12.5 points (P<0.05) between Screen and Control children with early vitamin E deficiency

	Control, α-T<300 (n=16)	Control, α-T≥300 (n=13)	Screen α-T<300 (n=17)	Screen, α-T≥300 (n=20)
CSI Mean (SD)	91.5 (15.1)	107.7 (15.4)	104.0 (16.2)	105.8 (15.0)

Summary of Evidence on Health Outcomes

- Moderate impact on growth – 0.3 Z-score difference in height-for-age
- Moderate impact on cognition – overall difference of 5-6 IQ points in WI study
- Reduction in CF-related child mortality is reported in studies at ~50% or more
- Reduction in hospitalization and cost is possible
- No consistent improvement in pulmonary outcomes and some risk of harm without adequate infection control